FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
October 17, 2012

Errata and Clarifications to the FDA Briefing Document - NDA 203858 (Lomitapide)

1. Page 23 of the Clinical Review, first bullet of the third paragraph:

Regarding CYP3A4 drug-drug interactions, the sponsor "proposed to address the CYP3A4 interaction in labeling; the package insert will indicate to avoid taking lomitapide with moderate or mild CYP3A4 inhibitors in addition to strong CYP3A4 inhibitors.

should be corrected to:

Regarding CYP3A4 drug-drug interactions, the sponsor "proposed to address the CYP3A4 interaction in labeling; the package insert will indicate to avoid taking ***moderate*** *CYP3A4 inhibitors in addition to strong CYP3A4 inhibitors* ***and labeling will caution about the use of lomitapide with mild CYP3A4 inhibitors****.*

2. Page 36 of the Clinical Review, first sentence of the second paragraph:

The efficacy and safety of lomitapide in the HoFH population was evaluated in one, single-arm, 78-week, phase 3 trial involving 28 subjects (hereafter, "HoFH-pivotal").

should be corrected to:

The efficacy and safety of lomitapide in the HoFH population was evaluated in one, single-arm, 78-week, phase 3 trial involving ***29*** *subjects (hereafter, "HoFH-pivotal").*

3. Page 43 of the Clinical Review, introductory paragraph of Section 5.2 (Exposure to Lomitapide):

A calculation error was identified in the applicant's enumeration of subjects in the lomitapide development program. The total number of subjects in phase 1 studies that were not included in pooled analyses was 70 (i.e., 14 in single-dose + 56 in multiple-dose studies), bringing the total number of subjects treated with oral doses of lomitapide to 915 (from 925) and the overall total to 1135 (from 1145). Note that these data exclude study CV145-003a, which was terminated early as a result of *B. cereus* contamination of drug product; a complete clinical study report was not submitted to the NDA.

Table 11 presents a summary of the number of subjects ever exposed to lomitapide during its development, categorized by the phase and type of study. Overall, a total of 925 subjects ever received a dose of lomitapide, either as monotherapy or combined

with other lipid-lowering drugs. Of these, 317 (34%) were enrolled in phase 1 protocols, 446 (48%) in controlled phase 2 protocols (4-12 weeks), 133 (14%) in uncontrolled phase 2 protocols (drug-drug interaction study and HoFH-pilot), and 29 (3%) in the HoFH-pivotal trial.

should be corrected to:

*Table 11 presents a summary of the number of subjects ever exposed to lomitapide during its development, categorized by the phase and type of study. Overall, a total of **915** subjects ever received a dose of lomitapide, either as monotherapy or combined with other lipid-lowering drugs. Of these, **307** (34%) were enrolled in phase 1 protocols, 446 (**49**%) in controlled phase 2 protocols (4-12 weeks), 133 (**15**%) in uncontrolled phase 2 protocols (drug-drug interaction study and HoFH-pilot), and 29 (3%) in the HoFH-pivotal trial.*

4. Page 44 of the Clinical Review, Table 13:

The "Any time" cells in the mean daily dose >60 column should be 0 and 0% (instead of 4 and 14%). A corrected table follows:

Table 13. Exposure to Lomitapide in HoFH-pivotal

	Mean Lomitapide Daily Dose							
Duration (days)	**≤5**	**(5, 10]**	**(10, 20]**	**(20, 40]**	**(40, 60]**	**>60**	**Any dose**	**%**
1-30	1	0	0	0	0	0	1	3%
31-91	2	0	1	0	0	0	3	10%
92-182	0	2	0	0	0	0	2	7%
183-365	0	0	0	0	0	0	0	0
366-545	0	1	3	5	4	0	13	45%
546-730	0	0	1	5	4	0	10	34%
Any time	3	3	5	10	8	**0**	29	100%
%	10%	10%	17%	35%	28%	**0%**	100%	

Source: 120-day safety update, Table 1.1.4A.
Notation: (10, 20] = 10 < dose ≤ 20

5. Page 117 of the Clinical Review, bullet #3:

Subject 01-004 was discontinued because of "physician decision," although the narrative reports that this was because of transaminases elevations that persisted despite graded dose reductions from 40 mg to 5 mg daily.

should be corrected to:

*Subject 01-004 was discontinued because of "**Sponsor decision**," although the narrative reports that this was because of transaminases elevations that persisted despite graded dose reductions from 40 mg to 5 mg daily.*

6. Pages 133-135 of the Clinical Review, Figures 28 and 29:

Subject 12-004 had a hepatic fat assessment by MRI on study day 1 (0.00%) and by MRS on study day 15 (5.01%). Both of these visits were marked as "Week 0" in the database, so the clinical reviewer's analyses inadvertently used the MRS value (given priority of MRS over MRI for a given visit) even though it occurred 2 weeks after starting study drug. This apparent increase in hepatic fat during the 2-week interval likely represents a true effect despite the difference in methodology. In the phase 2 study AEGR-733-004, lomitapide 5 mg daily increased hepatic fat by 5.5% absolute at week 4, compared with placebo, and this time point revealed the maximum increase observed during the 12-week trial.

Changing the baseline value for subject 12-004 from 5.0% to 0.0% affected Figures 28 and 29 in the clinical review. Note that the revised Figure 28 only includes subjects with at least one post-baseline assessment of hepatic fat.

Figure 28 should be corrected to the following:

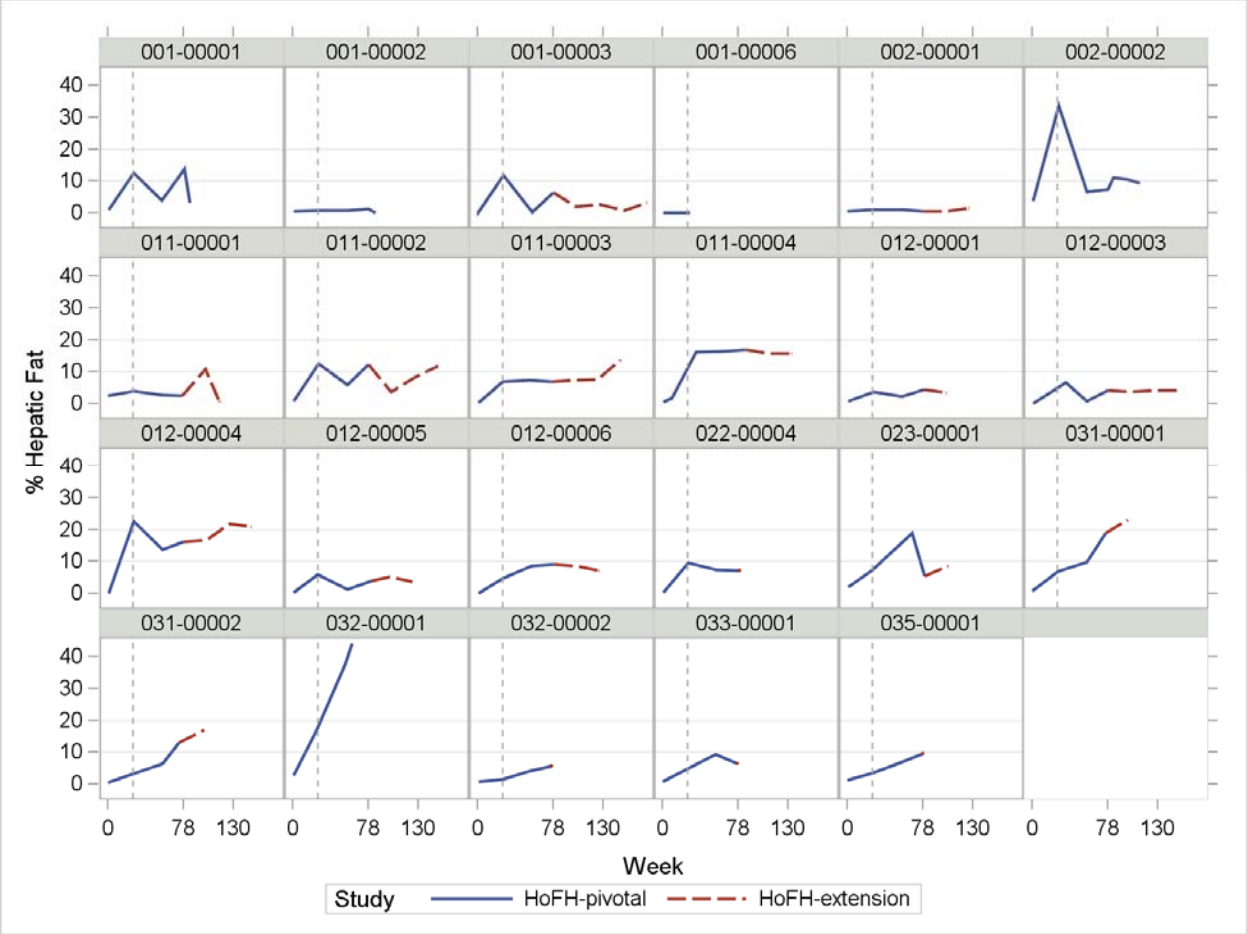

Figure 28. HoFH Phase 3 – % Hepatic Fat Profiles
Source: FDA clinical reviewer's analysis of submitted hepatic fat datasets from HoFH-pivotal and HoFH-extension (*OM.xpt*).
The dashed vertical lines indicate the end of the efficacy period (week 26) of HoFH-pivotal. Data may include off-treatment follow-up values (e.g., Subject 001-00001, whose last on-drug value was 13.9%).
This figure only includes subjects with at least one post-baseline value.

The text on page 134 of the Clinical Review should be corrected from:

To explore whether larger increases in hepatic fat during the study are associated with higher amounts of hepatic fat at baseline, I examined the association between % hepatic fat at baseline and at week 26. In a simple linear regression model, each 1% of hepatic fat at baseline was associated with a 4.7% absolute percentage point higher amount of hepatic fat at week 26 (R^2=57.4%, p=0.0001). This relationship is depicted in Figure 29.

to

*To explore whether larger increases in hepatic fat during the study are associated with higher amounts of hepatic fat at baseline, I examined the association between % hepatic fat at baseline and at week 26. In a simple linear regression model, each 1% of hepatic fat at baseline was associated with a 4.**6**% absolute percentage point higher amount of hepatic fat at week 26 (R^2=**32.1**%, p=**0.006**). This relationship is depicted in Figure 29.*

Figure 29 should be corrected to the following:

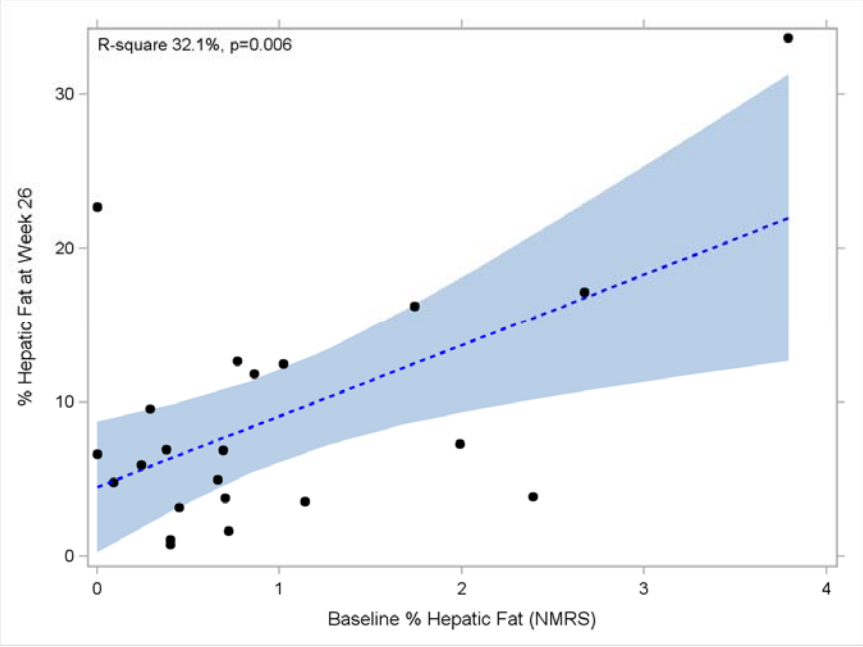

Figure 29. HoFH-pivotal – % Hepatic Fat at Baseline vs. Week 26
Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal dataset (*OM.xpt*).

7. Page 137 of the Clinical Review, Table 56:

The applicant identified a typographical error in their 17 August 2012 response to an FDA information request that was the source for Table 56. The hepatic fat measurement in the "Baseline" column for Subject 01-004 was obtained at approximately week **40** rather than week 4. Table 56 should be corrected to the following:

Table 56. HoFH-pivotal – Reversibility of Hepatic Fat

Subject	Baseline	Peak % Hepatic Fat on Study	% Hepatic Fat at Week 78	Follow-up
01-001	1%	14% at week 78	14%	3% (~6 wks post)
01-004	Mild-to-mod by CT ***at week 40***	Moderate by CT at week 78	Moderate by CT	Mild-to-moderate (~6 wks post)
01-006	0%	None	(Early DC after ~6 months)	0% (~2 wks post)
01-002	0.4%	1.1% at week 78	1.1%	0% (~7 wks post)
02-002	4%	34% at week 26	7%	11%, 11%, and 9% (~1, 6, 9 months post)
11-001	2%	11% at week 102 (extension)	2%	0.6% (~8 wks post)
32-001	3%	44%	Not Done	Mild (~7-15%) by CT (~6 wks post)

Source: 17 August 2012 response to FDA information request.

8. Page 194 of the Clinical Review, Figure 52:

Figure 52 should be corrected to the following:

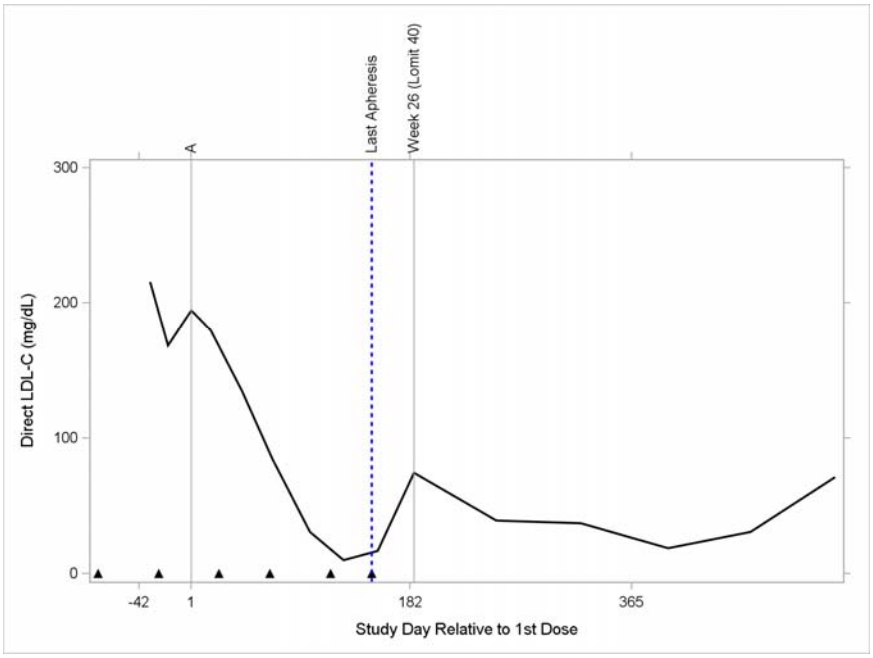

Figure 52. HoFH-pivotal – Subject 31-001 (Apheresis Discontinued)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) On simvastatin 20 mg and ezetimibe 10 mg daily throughout.